JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2009, p. 3914–3919 Vol. 47, No. 12
0095-1137/09/$12.00 doi:10.1128/JCM.00628-09

CD64 Index Provides Simple and Predictive Testing for Detection and Monitoring of Sepsis and Bacterial Infection in Hospital Patients▽†

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Received 27 March 2009/Returned for modification 17 July 2009/Accepted 2 October 2009

The rapid diagnosis and management of bacterial infection are heavily dependent upon clinical assessment. Blood culture may take up to 2 days for results and may be suspect. Surface neutrophil CD64 expression has been shown to be upregulated in cases of bacterial infection. Recently, a standardized kit for the CD64 index was used in neonatal intensive care units, showing high sensitivity and specificity for bacterial infections. Our study was designed to confirm and extend these results to adult hospital patients and to determine the impact of this testing on a clinical laboratory's finances and staffing. CD64 indices were performed with peripheral blood drawn in tandem with blood cultures from 109 patients over a 2-month period. We found that a CD64 index of ≤1.19 was predictive of "no growth" blood culture results. An index of >1.19 was predictive of an ultimate clinical and/or culture diagnosis of infection with a sensitivity and specificity of 94.6% and 88.7%, respectively. Positive and negative predictive values were 89.8% and 94%, respectively. The CD64 index was easily performed using our flow cytometer and staff, producing minimal alteration in clinical workflow. A 7-day-a-week testing schedule will result in some additional expense but will be more than offset by the expected cost savings. The CD64 index is a useful and inexpensive test for improving the diagnosis and management of hospital patients with bacterial infection. It can be readily performed by clinical laboratories and could result in considerable savings for the institution.

Current guidelines for treatment of severe sepsis promote rapid treatment with antibiotics (within 1 h of diagnosis) and localization of the primary infectious source within 6 h. This is followed by a reassessment of therapy at 24 h (7). Blood culture, the "gold standard" for detection of systemic infection, can take up to 2 days to reliably provide a "negative" result (22). Furthermore, blood cultures are dependent on the presence of bacteremia. Growth can be suppressed if blood cultures are drawn after initiation of antibiotic therapy (4, 24). Due to this delay and uncertainty, a care provider must often fall back on clinical symptoms and less predictive laboratory measures, such as fever or white blood cell (WBC) count, in an attempt to document the presence of infection. More recent markers such as C-reactive protein and procalcitonin have been used to increase diagnostic sensitivity and specificity (16). While improvements, these methods still suffer from confounding factors and false positives, which make them less than ideal (27, 28). Surface expression of CD64 (high-affinity Fcγ receptor) has been shown to increase in patients with bacterial infections (15). Several studies have indicated that the measurement of surface granulocyte CD64 may be useful in the detection of bacterial infection and sepsis in the workup of patients with systemic inflammatory response syndrome and fevers of unknown origin (1, 5, 9, 12–14, 17, 19–21, 23, 26, 30). Recently, two studies have demonstrated that CD64 measured as an index has high sensitivity and specificity for infection when used among neonatal intensive care unit patients (3, 11). We set out to see whether we could confirm and extend these findings among an adult general hospital population. Our goal was to determine if granulocyte expression has a significant correlation with "clinically" diagnosed bacterial infections and if granulocyte CD64 expression can predict the results of a patient's blood culture. We also sought to determine the amount of effort and expense that is required to integrate this test into a typical clinical flow cytometry laboratory and compare that to savings that would be expected to result from effective management.

MATERIALS AND METHODS

Samples studied. Residual EDTA blood samples from complete blood counts were obtained in all patients receiving a blood culture for a 2-month period. A total of 142 blood samples drawn within 36 h (mean of 4 h) of blood culture events in 113 patients were used for analysis. Two patients were excluded prior to performance of a CD64 index study due to granulocytopenia. Two additional patients were excluded after it was subsequently determined that these patients had received granulocyte colony-stimulating factor and Epogen therapy. The distribution of the patients is displayed in the study flowchart in Fig. 1. Additionally, 24 specimens from normal healthy individuals and 20 specimens from patients with uncomplicated surgeries were used for controls. All specimens were obtained and studied using a protocol approved by the Iowa City VA Hospital Institutional Review Board.

CD64 index. CD64 expression by granulocytes was measured using a Leuko64 kit (Trillium Diagnostics, ME) and a BD FACSCalibur running Quanticalc software (Verity Software House, ME). This test kit includes fluorescent beads and antibodies to CD64 and CD163. The patient's sample provides an internal negative control (lymphocytes) and an internal positive control (monocytes). The lymphocyte population is defined by forward and side scatter characteristics and is distinct from granulocytes. Surface CD163 staining along with forward and side scatter characteristics are used to define the monocyte population. The CD64 index is then calculated using the ratio of the mean fluorescent intensity of the cell populations to that of the beads. Lymphocytes must have a CD64 index of

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† Supplemental material for this article may be found at http://jcm.asm.org/.

▽ Published ahead of print on 21 October 2009.

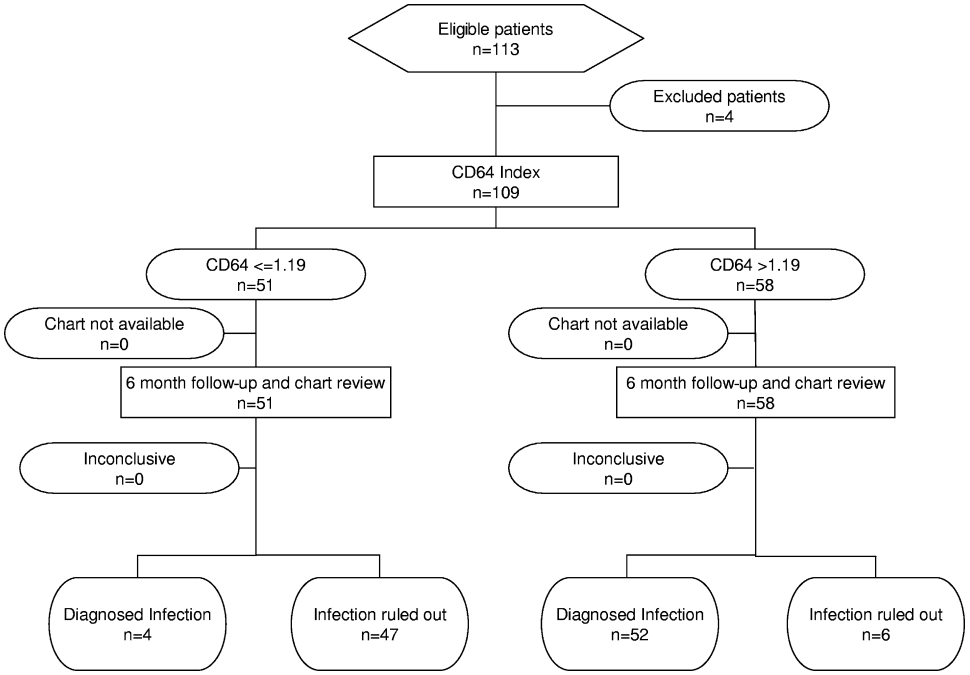

FIG. 1. Study flowchart.

<1 and monocytes an index of >3 for the internal controls to be considered valid. Control samples for the CD64 index were obtained from 24 healthy adult subjects, with a mixture of men and women of a wide age range. Samples from the healthy controls showed indices between 0.54 and 1.1 with a mean ± standard deviation of 0.73 ± 0.15. A second control group of 20 patients who had undergone a range of uncomplicated surgical procedures (11 total knee replacements, 5 abdominal surgeries, 1 partial lung resection, 1 glossectomy, 1 parotidectomy, and 1 axillary resection) was also studied. This group showed values between 0.45 and 1.1 with a mean ± standard deviation of 0.78 ± 0.16. A standard *t* test showed no statistical difference between this group and the normal controls with a *P* value of 0.25.

Precision studies were also conducted by performing 20 repetitions on three samples showing a mean coefficient of variation (CV) ± standard deviation of 1.7% ± 0.045%.

Blood cultures. Patient blood was cultured using a Bactec 9240 (Becton-Dickinson, MD). Standard hospital procedures with two culture sets (anaerobic and aerobic bottles) from two different sites were followed (16). Of the cultured events, 82% were paired cultures. Each set of cultures was considered 1 culture event for the purposes of our analysis.

Blood cultures were called positive according to a standard algorithm (2, 25). Briefly, a blood culture event was considered positive when more than one bottle of a set showed growth or a single bottle grew an isolate of bacteria not typically associated with skin contamination. A blood culture was said to be "false positive" when only one bottle was positive, the patient history did not suggest infection, and the organism was identified as a common contaminant. These patients were grouped with the "negative" blood culture results.

Chart review and clinical scoring. Patient records were examined to determine the clinical outcomes of the hospitalizations and assigned a clinical score denoting the likelihood of a bacterial infection with systemic symptoms. Four groups of patients were defined, and each patient was assigned to only one of the four groups (Table 1). Group 1 consisted of patients in which the clinical team was able to rule out a bacterial infection. Of these patients, 71% had a fever and/or altered WBC count at the time of their first blood culture. The clinical course of hospitalization and follow-up visits had no evidence of infection, and these patients were not assigned the diagnosis of infection by the clinical team. Group 2 consisted of patients in whom the clinical teams were unable to rule out bacterial infection. They were considered as having a "suspected infection" and treated with broad-spectrum antibiotics. Of these patients, 66% had fever and/or an abnormal WBC count at the time of first culture. While these patients lacked a definitive positive culture identification of a causative organism, they had strongly suggestive findings of bacterial infection on chest X-ray/computed tomography scans, physical examination, and/or the clinical course of hospitalization (e.g., history of aspiration, obvious induration, draining abscesses, or organisms seen by gram stains or biopsy). As a result, these patients were diagnosed with infection by their clinical teams. Group 3 consisted of patients with a positive culture from any source other than blood culture. Group 4 consisted of patients with positive blood cultures documenting bacteremia.

Statistical analysis. Means, standard deviations, and CVs of the CD64 index and WBC count were calculated for each group. Comparison of the four groups was made using two-tailed *t* tests, and the *P* values were calculated. A *P* value of <0.05 was considered significant. Receiver operating characteristic (ROC) curves were constructed for the CD64 index and WBC counts using EP Evaluator software (David G. Rhodes Assoc., PA). The point of maximum test efficiency, sensitivity, specificity, likelihood ratios, and positive and negative predictive values were calculated.

RESULTS

The distribution of positive and negative samples between patient groups, the CD64 index values, and results of the two tail *t* tests between the groups are displayed in Table 1 and Fig. 2. The

TABLE 1. Distribution of mean CD64 index and WBC samples between the four patient groups[a]

Group (characteristic)	No. of patients	Mean ± SD CD64 index value	Mean ± SD WBC count (10^3)
1 (no infection)	53	1.04 ± 0.85	9.76 ± 4.43
2 (clinical infection)	35	2.42 ± 1.98	11.00 ± 5.59
3 (culture-proven infection)[b]	9	2.00 ± 1.25	18.01 ± 9.82
4 (blood culture-proven infection)	12	4.84 ± 4.28	15.50 ± 14.80

[a] For statistical significance comparisons, CD64 *P* values are as follows: group 1 and control, $P = 0.09$; groups 1 and 2, $P = 0.000019$; groups 2 and 3, $P = 0.55$; groups 3 and 4, $P = 0.07$; and group 1 versus groups 2, 3, and 4, $P = 0.000008$. Supplemental Tables S1 and S2 detail the major dignoses and the cultured organisms of the patient groups.

[b] Excludes blood culture-positive patients.

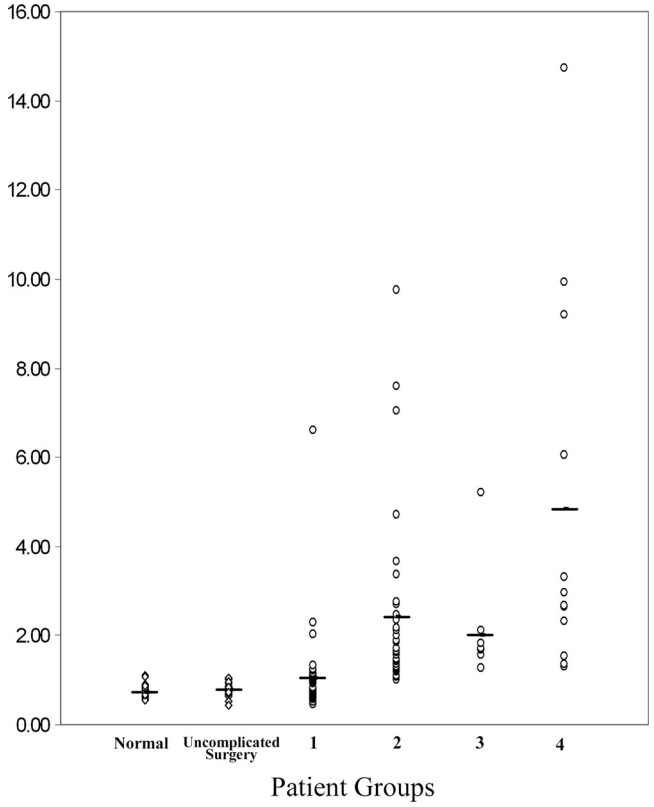

FIG. 2. Dot plot of the CD64 index distribution between the "normal" nonhospitalized controls, uncomplicated surgery patients, and the four patient groups. Mean values are indicated by the horizontal lines.

control population and group 1 (patients without infection) were not statistically different from each other ($P = 0.09$). Groups 2 (clinically diagnosed infection), 3 (culture-proven infection), and 4 (culture-proven bacteremia) also were not statistically different from each other. Comparison of group 1 to the combined groups 2 through 4 gave a P value of 0.000008. An ROC curve for group 1 (noninfected) versus combined groups 2 through 4 (infected) is shown in Fig. 3A. Maximal efficiency was seen at a cutoff value of 1.19, with a P value of 0.000019. A CD64 index of >1.19 had a sensitivity and specificity for infection of 94.6% and 88.7%, respectively. The positive and negative likelihood ratios were 8.36 and 0.06. The positive and negative predictive values were 89.8% and 94%.

If a CD64 index value of 1.19 was used as a cutoff for "infection," 53 patients were negative (not infected) and 56 were positive (infected). Of the 53 CD64-negative patients, none had a positive bacterial culture from any source while 6 had false-positive cultures. Four were false-positive blood cultures, one was a false-positive pleural fluid, and one was a false positive spinal fluid. Of the 56 positive patients, 12 had positive blood cultures and 9 had positive cultures from other sites.

In comparison, the WBC count showed a maximal efficiency at $9.2 \times 10^3/\text{mm}^3$ and had a sensitivity and specificity of 69.6 and 52.8. Its positive and negative likelihood ratios were 1.48 and 0.57, with positive and negative predictive values of 60.9% and 62.2%. Comparison of the areas under the ROC curve for CD64 index (0.943) and WBC count (0.626) showed the CD64 index to be far superior (Fig. 3B and C).

While our study was not designed to look specifically at the change in CD64 index in response to antibiotic therapy, 16 of our patients received multiple cultures during the 2-month time span. The changes in CD64 index observed confirmed those reported previously (8, 10, 18). Patients receiving adequate antibiotic therapy had quick reduction in their CD64 indices after 2 to 3 days which correlated with a decrease in the patient's clinical symptoms of sepsis. One patient, who was successfully treated for an infection present on admission, subsequently acquired a nosocomial infection. This patient's CD64 index once again became elevated. After a restart of antibiotics, the CD64 index again decreased (Fig. 4).

DISCUSSION

Given the prior literature and two recent studies in pediatric populations, there is strong evidence that granulocyte CD64 expression represents a promising screening test for infection (3, 6, 8, 11, 14, 20). Studies have compared patients with culture-proven infections and/or severe sepsis against control subjects in order to determine if antibiotics should be given to a patient or not. While very encouraging, they have not effectively simulated the actual clinical decision-making process of managing typical hospital patients with suspected infections. Blood cultures, which are the gold standard for diagnosing systemic infection, present a unique problem as the turnaround time of this test is highly variable. "Positive" results are typically available at 24 h for the reassessment of antibiotic therapy, whereas "negative" results are not. A clinical problem arises when a patient has clinical signs and symptoms compatible with sepsis, yet has a blood culture result of "pending."

Our study was designed to see if we could confirm and extend the previous literature on neutrophil CD64 expression. We sought to determine whether the level of CD64 expression is predictive of significant bacterial infections in the hospital setting, to ascertain the predictive ability of CD64 expression for final blood culture, and to determine what efforts would be required by the hospital laboratory to implement this testing. These three points would be vital to determining the utility of neutrophil CD64 testing in clinical, laboratory, and pharmacy algorithms to promote better antibiotic management and resource utilization.

A result of >1.19 provided prediction of a final diagnosis of infection. At this level, it not only detected all of the culture-positive patients, but it also identified those in whom a final clinical diagnosis of infection was made. Of the 35 patients who were diagnosed with infection without a positive culture (group 2), 88% had a CD64 index above 1.19. The CD64 index was >1.19 in all 21 cases (groups 3 and 4) in which a causative organism could be culture identified.

Examination of the four group 2 patients with a CD64 index below 1.19 showed that they all were receiving antibiotic therapy and had limited systemic symptoms. One was a patient with chronic osteomyelitis under intravenous antibiotic therapy, two were patients with localized wound infections treated with debridement and antibiotics, and the final patient had a possible abdominal abscess due to Crohn's disease. All four were started on antibiotic therapy prior to the beginning of our

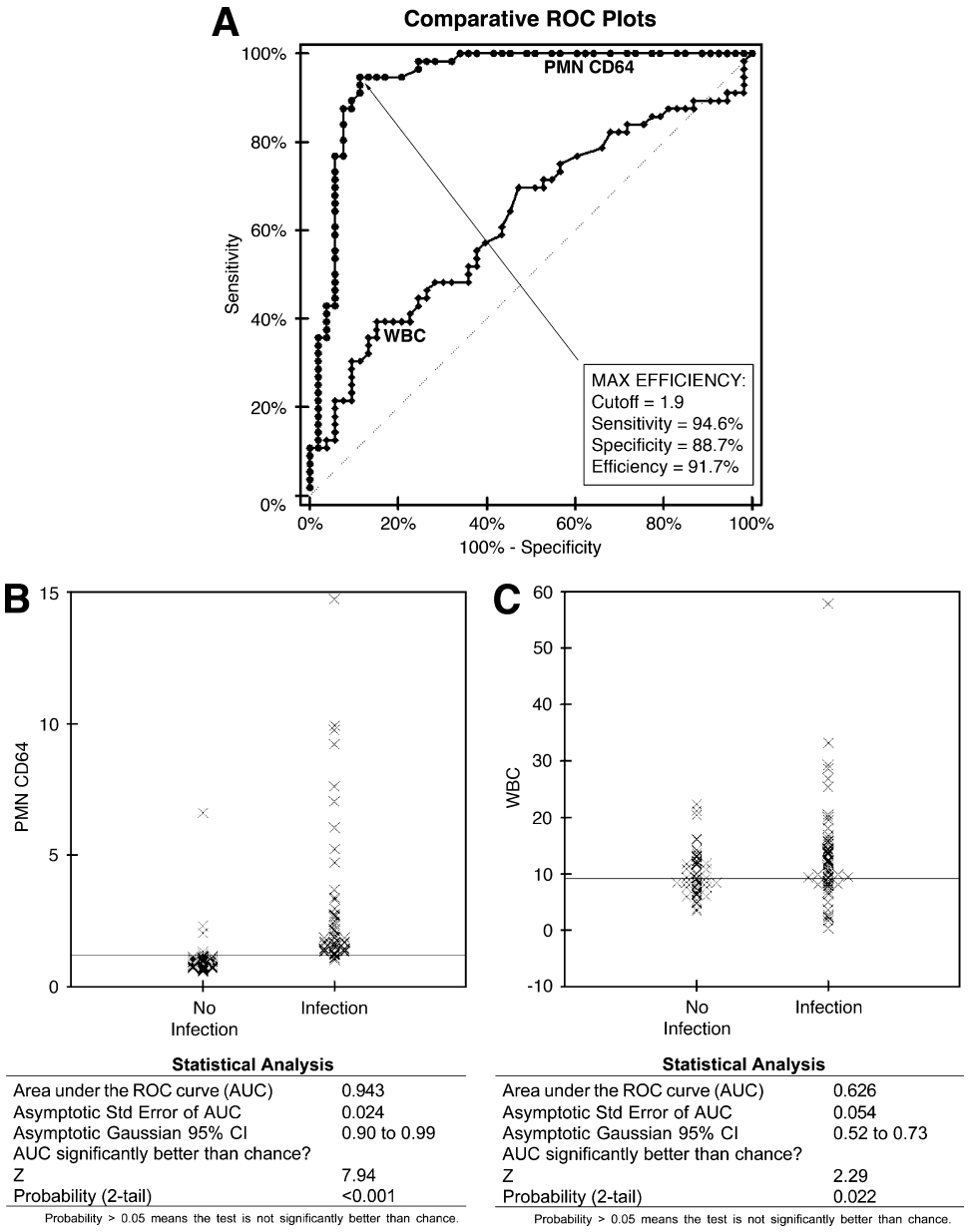

FIG. 3. (A) Comparative ROC curves for WBC count and CD64 index; (B) distribution of CD64 index values in the noninfected and infected patient groups; (C) distribution of WBC count values (10^3) in the noninfected and infected patient groups. PMN, polymorphonuclear leukocyte; Std, standard; CI, confidence interval.

study and recovered under antibiotic therapy. In this situation, a normal index may indicate treatment is adequate to prevent a systemic response.

A CD64 index of ≤1.19 was 100% predictive of a "no-growth" blood culture. None of our patients with a normal CD64 index had a true-positive blood culture. Seven "false-positive" cultures were present in the studied patient population (five blood cultures, a pleural fluid culture, and a spinal fluid culture). Only one of these cases had a CD64 index above 1.19. This particular patient presented with atrial fibrillation and emesis and had 1 of 4 blood culture bottles grow *Staphylococcus capitus*. After ruling out a myocardial infarction, the patient was discharged without receiving antibiotic therapy. The clinical team did not feel that this patient's presenting symptoms were related to infection; however, the precise cause was never determined.

A CD64 index of ≤1.19 was specific for a "no-growth" blood culture, provided prediction of a final "rule out" of a bacterial infection by the clinical team, and was useful in identifying false-positive cultures.

While it is clear that the CD64 index is a promising test for the detection and monitoring of antimicrobial therapy, there is the practical limitation that this test must be performed on a flow cytometer. This requires access both to a flow cytometer and an operator. Typically, flow cytometers are located in labs which operate only from 9:00 a.m. to 5:00 p.m. on weekdays.

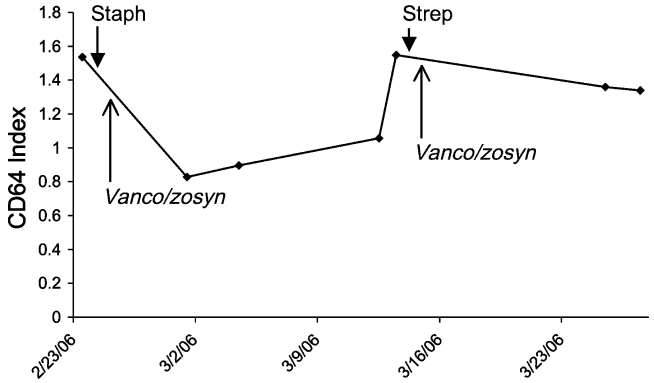

FIG. 4. Multiple CD64 index measurements in a patient receiving adequate antibiotic therapy and then acquiring a nosocomial infection. Staph, *Staphylococcus*; Strep, *Streptococcus*; *Vanco*, vancomycin; *zosyn*, Zosyn (piperacillin and tazobactam).

The addition of a test that requires availability 24 h/day for 7 days/week implies that considerable restructuring of these laboratories would be necessary. One of our goals in conducting this study was to evaluate if we could integrate this testing into regular, daily flow cytometry workload and determine what additional staffing and expense would be required of the laboratory.

In considering the guidelines from the Surviving Sepsis Campaign (7), patients with severe sepsis need to receive antibiotics within 1 h. It is difficult to provide all of the necessary lab data within this time frame; thus, patients are often treated empirically. The next decision point is a reassessment of antibiotic therapy at 24 h, when some blood cultures will still be listed as "pending." Having a flow cytometric CD64 result available at this time is not problematic. If negative, it indicates that bacteremia is not present and that the discontinuation of antibiotics can be considered. For this, once-daily testing can suffice. The need for additional staff is minimal. For most laboratories, it would involve adding 2 half-days to their schedules to cover weekends. This should be manageable for most, even considering the difficulties in finding laboratory technologists trained in flow cytometry.

As the measurement of neutrophil CD64 is a quantitative flow cytometric assay, a method with much more rigorous standardization than the typical qualitative flow cytometric tests is necessary. Review of the existing literature showed that different anti-CD64 antibodies, different types of flow cytometers, and different measured parameters for neutrophil CD64 have been used (1, 5, 9, 12–15, 17, 19–21, 23, 26, 30). Some of these required a fairly experienced operator conducting the testing. Since all of these factors have a significant impact on the reproducibility and the interpretation of quantitative flow cytometry results, direct comparison of these studies was difficult. Since our study involved a fairly lengthy specimen collection period (2 months), lot-to-lot variability of the fluorescent-labeled antibodies and differing operator skill levels needed to be considered. To reduce these sources of variability, we elected to use Trillium Diagnostic's Leuko64 assay. This testing kit provides the rigorous internal standardization required for quantitative assays by incorporating fluorescent beads and antibodies which have been standardized for several models of flow cytometers. This information is then updated into the Quanticalc software with each antibody lot, ensuring lot-to-lot consistency. This software also provides for automated analysis, simplifying the test and reducing interoperator variability. As a result, the highly developed skill set required for the quantitative analysis of oncologic specimens was not necessary for determination of the CD64 index. The consensus of our technical staff was that this test was similar to the CD4 T-cell subset enumeration kits commonly performed for acquired immunodeficiencies. The time needed to perform a Leuko64 test was less than that for T-cell subsetting, with a total tech time of 45 min, the majority of this being consumed by two incubation steps totaling 30 min. Also, techs with only minimal training in the operation of a flow cytometer were able to produce consistent, high-quality results.

In total, the cost to our laboratory including consumables, wages, and equipment depreciation is under $10.00 per test. We understand that not all institutions will have similar costs, but for our hospital patients, changing the antibiotics prescribed for only 2 of the 112 patients we tested would have paid for all 142 tests we performed. Simply catching the false-positive blood cultures and avoiding performance of unnecessary organism typing and antibiotic screening would have paid for over 75% of the tests.

If a negative test were used to stop administration of antibiotics at 24 h in group 1 (noninfected) patients, it would have resulted in a savings of 98 days of broad-spectrum IV antibiotics, or roughly $32,000: a 20% reduction in the cost of antibiotics used by the study patients in the 2-month period. This would represent $192,000 a year in potential savings and is without considering the cost of nursing care, bed charges, treatment complications, and antibiotic resistance. The expense of performing the CD64 index is therefore more than compensated for by the potential savings generated.

As a result, our laboratory is offering 7-day-a-week, once-a-day testing with the CD64 index and we have begun to evaluate the test for our postoperative surgical patients.

As many modern hematology analyzers contain flow cytometers and are capable of doing CD4 subsetting, incorporation of CD64 index testing into these platforms will further simplify this test. It has already been demonstrated that modern hematology analyzers can perform this test with reliable results (29), and at least two companies have produced analyte-specific reagent kits for their analyzers. This should allow performance of this test by those with no experience with standalone flow cytometers. STAT testing, in core laboratories, could be performed on the specimens already drawn for WBCs, making a high-quality result available at the time of the initial decision to administer antibiotics.

The CD64 index is a useful test for the detection and management of sepsis and significant bacterial infection. Using a cutoff of >1.19, the test is highly sensitive and specific for a final diagnosis of infection. A CD64 index of ≤ 1.19 can predict a negative blood culture result and identify false-positive results. It can be performed with specimens, equipment, and personnel already present in large medical centers and can be brought into additional hospitals as they modernize their hematology analyzers. The potential cost savings from improving antibiotic management and reducing antibiotic resistance and treatment complications more than compensate for the mate-

rial and personnel expenses to the institution. The CD64 index is ready to be performed in clinical laboratories and to be added to criteria used to diagnose infection.

REFERENCES

1. **Barth, E., G. Fischer, E. M. Schneider, J. Wollmeyer, M. Georgieff, and M. Weiss.** 2001. Differences in the expression of CD64 and mCD14 on polymorphonuclear cells and on monocytes in patients with septic shock. Cytokine **14:**299–302.
2. **Beekmann, S. E., D. J. Diekema, and G. V. Doern.** 2005. Determining the clinical significance of coagulase-negative staphylococci isolated from blood cultures. Infect. Control Hosp. Epidemiol. **26:**559–566.
3. **Bhandari, V., C. Wang, C. Rinder, and H. Rinder.** 2008. Hematologic profile of sepsis in neonates: neutrophil CD64 as a diagnostic marker. Pediatrics **121:**129–134.
4. **Darby, J. M., P. Linden, W. Pasculle, and M. Saul.** 1997. Utilization and diagnostic yield of blood cultures in a surgical intensive care unit. Crit. Care Med. **25:**989–994.
5. **Davis, B. H., and N. C. Bigelow.** 2005. Comparison of neutrophil CD64 expression, manual myeloid immaturity counts, and automated hematology analyzer flags as indicators of infection or sepsis. Lab. Hematol. **11:**137–147.
6. **Davis, B. H., S. H. Olsen, E. Ahmad, and N. C. Bigelow.** 2006. Neutrophil CD64 is an improved indicator of infection or sepsis in emergency department patients. Arch. Pathol. Lab. Med. **130:**654–661.
7. **Dellinger, R. P., M. M. Levy, J. M. Carlet, J. Bion, M. M. Parker, R. Jaeschke, K. Reinhart, D. C. Angus, C. Brun-Buisson, R. Beale, T. Calandra, J. F. Dhainaut, H. Gerlach, M. Harvey, J. J. Marini, J. Marshall, M. Ranieri, G. Ramsay, J. Sevransky, B. T. Thompson, S. Townsend, J. S. Vender, J. L. Zimmerman, and J. L. Vincent.** 2008. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit. Care Med. **36:**296–327.
8. **Fischer, G., E. M. Schneider, L. L. Moldawer, C. Karcher, E. Barth, H. Suger-Wiedeck, M. Georgieff, and M. Weiss.** 2001. CD64 surface expression on neutrophils is transiently upregulated in patients with septic shock. Intensive Care Med. **27:**1848–1852.
9. **Fjaertoft, G., L. Hakansson, U. Ewald, T. Foucard, and P. Venge.** 1999. Neutrophils from term and preterm newborn infants express the high affinity Fcgamma-receptor I (CD64) during bacterial infections. Pediatr. Res. **45:** 871–876.
10. **Fjaertoft, G., L. D. Hakansson, K. Pauksens, G. Sisask, and P. Venge.** 2007. Neutrophil CD64 (FcgammaRI) expression is a specific marker of bacterial infection: a study on the kinetics and the impact of major surgery. Scand. J. Infect. Dis. **39:**525–535.
11. **Groselj-Grenc, M., A. Ihan, and M. Derganc.** 2008. Neutrophil and monocyte CD64 and CD163 expression in critically ill neonates and children with sepsis: comparison of fluorescence intensities and calculated indexes. Mediators Inflamm. **2008:**202646.
12. **Hirsh, M., E. Mahamid, Y. Bashenko, I. Hirsh, and M. M. Krausz.** 2001. Overexpression of the high-affinity Fcgamma receptor (CD64) is associated with leukocyte dysfunction in sepsis. Shock **16:**102–108.
13. **Hoffmeyer, F., K. Witte, and R. E. Schmidt.** 1997. The high-affinity Fc gamma RI on PMN: regulation of expression and signal transduction. Immunology **92:**544–552.
14. **Layseca-Espinosa, E., L. F. Perez-Gonzalez, A. Torres-Montes, L. Baranda, H. de la Fuente, Y. Rosenstein, and R. Gonzalez-Amaro.** 2002. Expression of CD64 as a potential marker of neonatal sepsis. Pediatr. Allergy Immunol. **13:**319–327.
15. **Leino, L., K. Sorvajarvi, J. Katajisto, M. Laine, E. M. Lilius, T. T. Pelliniemi, A. Rajamaki, P. Silvoniemi, and J. Nikoskelainen.** 1997. Febrile infection changes the expression of IgG Fc receptors and complement receptors in human neutrophils in vivo. Clin. Exp. Immunol. **107:**37–43.
16. **Levy, M. M., M. P. Fink, J. C. Marshall, E. Abraham, D. Angus, D. Cook, J. Cohen, S. M. Opal, J. L. Vincent, and G. Ramsay.** 2003. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit. Care Med. **31:**1250–1256.
17. **Livaditi, O., A. Kotanidou, A. Psarra, I. Dimopoulou, C. Sotiropoulou, K. Augustatou, C. Papasteriades, A. Armaganidis, C. Roussos, S. E. Orfanos, and E. E. Douzinas.** 2006. Neutrophil CD64 expression and serum IL-8: sensitive early markers of severity and outcome in sepsis. Cytokine **36:**283–290.
18. **Matsui, T., K. Ohsumi, N. Ozawa, K. Shimada, S. Sumitomo, K. Shimane, M. Kawakami, H. Nakayama, S. Sugii, Y. Ozawa, and S. Tohma.** 2006. CD64 on neutrophils is a sensitive and specific marker for detection of infection in patients with rheumatoid arthritis. J. Rheumatol. **33:**2416–2424.
19. **Ng, P. C., G. Li, K. M. Chui, W. C. Chu, K. Li, R. P. Wong, K. W. Chik, E. Wong, and T. F. Fok.** 2004. Neutrophil CD64 is a sensitive diagnostic marker for early-onset neonatal infection. Pediatr. Res. **56:**796–803.
20. **Ng, P. C., K. Li, R. P. Wong, K. M. Chui, E. Wong, and T. F. Fok.** 2002. Neutrophil CD64 expression: a sensitive diagnostic marker for late-onset nosocomial infection in very low birthweight infants. Pediatr. Res. **51:**296–303.
21. **Nuutila, J., U. Hohenthal, I. Laitinen, P. Kotilainen, A. Rajamaki, J. Nikoskelainen, and E. M. Lilius.** 2007. Simultaneous quantitative analysis of FcgammaRI (CD64) expression on neutrophils and monocytes: a new, improved way to detect infections. J. Immunol. Methods **328:**189–200.
22. **Peters, R. P., M. A. van Agtmael, S. A. Danner, P. H. Savelkoul, and C. M. Vandenbroucke-Grauls.** 2004. New developments in the diagnosis of bloodstream infections. Lancet Infect. Dis. **4:**751–760.
23. **Qureshi, S. S., S. M. Lewis, V. A. Gant, D. Treacher, B. H. Davis, and K. A. Brown.** 2001. Increased distribution and expression of CD64 on blood polymorphonuclear cells from patients with the systemic inflammatory response syndrome (SIRS). Clin. Exp. Immunol. **125:**258–265.
24. **Reimer, L. G., M. L. Wilson, and M. P. Weinstein.** 1997. Update on detection of bacteremia and fungemia. Clin. Microbiol. Rev. **10:**444–465.
25. **Richter, S. S., S. E. Beekmann, J. L. Croco, D. J. Diekema, F. P. Koontz, M. A. Pfaller, and G. V. Doern.** 2002. Minimizing the workup of blood culture contaminants: implementation and evaluation of a laboratory-based algorithm. J. Clin. Microbiol. **40:**2437–2444.
26. **Simms, H. H., and R. D'Amico.** 1994. Regulation of intracellular polymorphonuclear leukocyte Fc receptors by lipopolysaccharide. Cell. Immunol. **157:**525–541.
27. **Tang, B. M., G. D. Eslick, J. C. Craig, and A. S. McLean.** 2007. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect. Dis. **7:**210–217.
28. **Uzzan, B., R. Cohen, P. Nicolas, M. Cucherat, and G. Y. Perret.** 2006. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Crit. Care Med. **34:**1996–2003.
29. **van der Meer, W., L. van Dun, J. K. Gunnewiek, B. Roemer, and C. S. Scott.** 2006. Simultaneous determination of membrane CD64 and HLA-DR expression by blood neutrophils and monocytes using the monoclonal antibody fluorescence capability of a routine haematology analyser. J. Immunol. Methods **311:**207–219.
30. **Wagner, C., R. Deppisch, B. Denefleh, F. Hug, K. Andrassy, and G. M. Hansch.** 2003. Expression patterns of the lipopolysaccharide receptor CD14, and the FCgamma receptors CD16 and CD64 on polymorphonuclear neutrophils: data from patients with severe bacterial infections and lipopolysaccharide-exposed cells. Shock **19:**5–12.